REMARKS

The rejections of Claims 1-5 and 7-12:

under 35 U.S.C. § 103(a) as obvious over "the combined teachings" of WO 97/11068 and US 5,998,436, each to Yazaki et al,[1] and

under the judicially created doctrine of obvious-type double patenting over Claims 1-11 of Yazaki et al (U.S.),

are respectfully traversed.

The present invention, as recited in Claim 1, is drawn to 1-(6-amino-3,5-difluoropyridin-2-yl)-8-bromo-7-(3-ethylaminoazetidin-1-yl)-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid or a salt thereof. In the specification, the acid (compound 1) and the maleate salt thereof (compound 2) are compared to compounds falling under the genus of compounds under Yazaki et al, but differing from the compounds of the present invention in that in comparative compound 1, (3-**methyl**aminoazetidin-1-yl) is substituted for (3-**ethyl**aminoazetidin-1-yl) in the compound of the present invention and in comparative compound 2, (8-**chloro**) is substituted for (8-**bromo**) in the compound of the present invention (emphasis added).

The antimicrobial effects, i.e., minimum growth inhibitory concentrations (MICs: g/mL) were determined and the results are set forth on Table 1 on page 22 of the specification. The minimum inhibitory concentration (MIC) of compound 1 was approximately half of that needed for comparative compound 1 and comparative compound 2 to inhibit MRSE W200; one half to inhibit S.epidermidis IFO 12293 for compound 1 versus comparative compound 1 and comparative compound 2; one half for E.faecalis IFO 12580 for compound 1 versus comparative compound 2; one half for M.luteus IFO 12708 for compound 1 versus comparative compound 2; one half for B.subtilis ATCC 6633 for

[1] WO 97/11068 and US 5,998,436 are from the same patent family, so their "combined teachings" is somewhat meaningless. Thus, citation in the text to Yazaki et al will be to column and line of US 5,998,436.

compound 1 versus comparative compound 1; one half for P.vulgaris IFO 3167 for compound 1 versus comparative compound 2. Thus, compound 1 of the present claims exhibits superior antimicrobial effects, as compared to comparative compounds under the genus of Yazaki et al, against numerous microbes by indicating much lower minimum growth inhibitory concentrations are necessary.

A phototoxicity test was performed on mice and the results of the comparison between compound 1 of the present invention and comparative compound 1 and comparative compound 2, are shown in Table 2 on page 23 of the specification. Compound 1 of the present invention shows no ear abnormality and with none of three animals showing ear abnormality, while comparative compound 2 shows 0.7, or mild erythema, in 2 out of 3 animals at 0 hour. Therefore, compound 1 of the present invention shows superior or equal resistance to phototoxicity, as compared to a comparative compound under the genus of Yazaki et al.

Antibacterial effects on clinically-isolated quinolone resistant pneumococci were determined for compound 1 of the present invention against comparative compound 2, a compound under the genus of Yazaki et al. The results are shown in Table 3 on page 23 of the specification. Compound 1 of the present invention showed minimum growth inhibitory concentrations (MICs; μg/mL) of one half for compound 1 of the present invention against comparative compound 1 for isolated coccus 1 and less than one-fourth for compound 1 against comparative compound 1 for isolated coccus 5. Therefore, superior results are shown for compound 1 of the present invention against a comparative compound under the genus of Yazaki et al by showing much lower minimum growth inhibitory concentrations are necessary.

Finally, an *in vivo* pharmacokinetic study was made on the absorption and excretion of the compounds of the present invention and comparative compounds in and from dogs,

specifically male beagles. The results are shown in Table 4 on page 25 of the specification. Compounds 1 and 2 of the present invention are compared to comparative compound 1 and the maleate salt of comparative compound 1, both compounds under the genus of Yazaki et al, with the maleate salt of comparative compound 1 being compared to compound 2, which is the maleate salt of compound 1 of the present invention. C_{max}(μg/mL) indicates a much higher concentration of the compounds of the present invention in the serum of the dogs after administration than that of the comparative compounds. The area under the serum concentration-time curve (AUC in μg.hr/mL) shows significantly higher values for the compounds of the present invention, as compared to the comparative compounds and the urinary excretion rate (%) is higher for the compounds of the present invention as compared to the comparative compounds. Thus, it can be seen that use of the compounds of the present invention results in much higher concentrations of the tested compounds in the serum within a comparable time period for the compounds of the present invention versus the comparative compounds with a significantly longer elimination half-life ($T_{½}$) for compound 1 versus comparative compound 1 and with a superior area under serum concentration-time curve (AUC) for the compounds of the present invention versus the comparative compounds and with an improved urinary excretion rate (%) for the compounds of the present invention as versus the comparative compounds. Therefore, the compounds of the present claims distinguish over Yazaki et al, because of the superior results shown above for compounds of the present invention, as compared to compounds falling under the genus of Yazaki et al, but different from the compounds of the present invention.

The presently-claimed invention is described as being an improvement over Yazaki et al. See the specification at page 2, line 8 through page 3, line 10. The pyridone carboxylic acid derivatives embraced by formula (I) of Yazaki et al number millions, if not more, of possible compounds. Of these possible compounds, Yazaki et al exemplify the preparation of

102 compounds, and the testing for antibacterial action and phytotoxicity for of four of them, i.e., Examples 9, 10, 12 and 39. The compounds of these four examples differ from the presently-claimed compound as follows: Example 9 contains a 3-aminoazetidin-1-yl group at the 7-position and chloro at the 8-position; Example 10 contains a 3-methylkaminoazetidin-1-yl at the 7-position and chloro at the 8-position; Example 12 contains a 3-hydroxyazetidine-1-yl at the 7-position and chloro at the 8-position; and Example 39 contains a 3-aminoazetidin-1-yl at the 7-position. It is clear that the above-discussed comparative compound 1 and comparative compound 2 described in the specification is closer to the claimed invention than any of the tested compounds of Yazaki et al. The Examiner relies on Example 75 and Claim 9 of Yazaki et al. Example 75 differs from the presently-claimed invention at both the 1-position, i.e., it has 6-amino-5-fluoropyridin-2-yl, and at the 7-position, i.e., it has a 3-methylaminoazetidin-1-yl. The compound of Claim 9 is identical to above-discussed comparative compound 1 herein. Of course, the compound of Claim 9 is not disclosed in Yazaki et al as having been tested.

To the extent the Examiner holds that the presently-claimed invention is *prima facie* obvious over the compounds of Yazaki et al because it falls within the broad genus of Yazaki et al, Applicants respectfully disagree since, as discussed above, Yazaki et al reads on literally millions of, if not more, compounds. Compare *In re Baird*, 29 USPQ 2d 1550 (Fed. Cir. 1994). To the extent the Examiner finds that the presently-claimed compound is *prima facie* obvious over the Claim 9 compound of Yazaki et al, which would appear to be the closest prior art compound of those disclosed by Yazaki et al, the above-discussed comparative data for comparative compound 1 demonstrates unexpected results. Indeed, the data in Table 3 and Table 4, by itself, demonstrates such results. Applicants describe the efficacy of their claimed invention in the specification at page 26, lines 6-21, as follows:

> Compound 1 and its salts according to the present invention have characteristic properties that, when administerd orally, they exhibit long

> blood half-time and extremely high bioavailability while retaining the properties that they are extremely high in antimicrobial effects and low in toxicity. Compound 1 and its salts also have excellent properties that they are lower in antihypertensive effect and side effects to skin, such as eruption, than known compounds of similar structures. Compound 1 and its salts, therefore, can be used widely as preventives and therapeutics for various infectious diseases of human and animals and also as fish drugs, agrichemicals, food preservatives and the like. Further, Compound 1 of the present invention is expected to have antiviral effects, especially anti-HIV (human immunodeficiency virus) effects, and is considered to be effective for the prevention or treatment of AIDS.

Finally, the viability of the above-discussed comparative data is supported by the newly-submitted Declaration.

For all the above reasons, it is respectfully requested that the above rejections be withdrawn.

The rejections of Claims 3, 5 and 7 under 35 U.S.C. § 101 and 35 U.S.C. § 112, are respectfully traversed. Claims 3 and 5 have been cancelled. Claim 7, contrary to the finding by the Examiner, is drafted in terms of a method, not a use.

For all the above reasons, it is respectfully requested that these rejections be withdrawn.

The rejection of Claims 7, 11 and 12 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. The newly-submitted Declaration rebuts the Examiner's findings that one skilled in the art would not be enabled to treat other than bacterial infections. To the extent that it is known that compounds having the basic skeleton of quinolinecarboxylic acid are known as antimicrobial compounds broadly, one skilled in the art would be enabled to use the presently-claimed compounds similarly. Accordingly, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 1-5 under 35 U.S.C. § 112, second paragraph, is respectfully traversed. The rejection would now appear to be moot. Accordingly, it is respectfully requested that it be withdrawn.

Regarding the Examiner's requirement of naming the first inventor between Yazaki et al and the present application, the Examiner should note that the respective inventive entities are the same.

All of the presently pending and active claims in this application are now believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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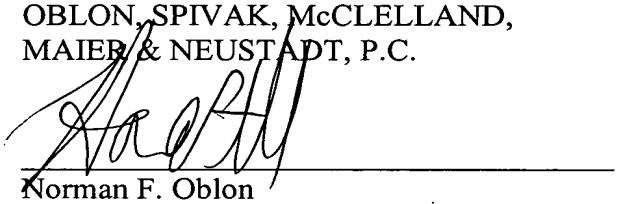

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